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Chelation-control in the formal [3+3] cyclization of 1,3-bis-(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-hex-4-en-3-ones. One-pot synthesis of 3-aryl-3,4-dihydroisocoumarins

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ABSTRACT

The [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-hex-4-en-3-ones resulted in the one-pot formation of 3-aryl-3,4-dihydroisocoumarins. The reactions proceeded by regioselective cyclization to give 6-(2-aryl-2-chloroethyl)salicylates, which underwent a silica gel-mediated lactonization. The cyclizations of protected 1-amino-5-silyloxy-hex-4-en-3-ones proved to be not regioselective.

1. Introduction

3-Aryl-3,4-dihydroisocoumarins (3-aryl-isochroman-1-ones) constitute a pharmacologically important chemical entity, which occurs in several natural products. This includes, for example, thunberginol C, D, and E and hydrangenol.[1a–c] Pharmacological activities of these natural products include promotion of the adipogenesis of murine 3T3-L1 cells,[1a] and show antiproliferative activity against mouse splenocytes[1b] and activity against human gastric cancer cell lines.[1c] Other 3-aryl-3,4-dihydroisocoumarins[1d] show antifungal activity,[1e] inhibition of rat basophilic leukaemia RBL-2H3 cells,[1f] antiproliferative activity against C57/BL6 mouse splenocytes,[1b] antiallergic activity,[1g] induction of steroidogenesis,[1h] phagocytic activity,[1i] immunomodulatory activity on spleen lymphocyte proliferation (activated by lipopolysaccharide, concanavalin A and phytohaemagglutinin in mice) [1j] and antimicrobial activity.[1k–m,2] In a number of natural products, one of the hydroxyl groups of the 3-aryl-3,4-dihydroisocoumarin core structure is glycosylated; this includes, for example, (−)-hydrangenol 4′-*O*-glucoside[1i] and phyllodulcin 8-*O*-glucoside.[1a,1l]

Formal [3+3] cyclization reactions[3,4] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[5] with 3-silyloxy-2-en-1-ones provide a versatile method for the synthesis of various functionalized arenes and hetarenes. However, this method is mainly limited to cyclizations of 3-silyloxy-2-en-1-ones derived from symmetrical 1,3-diketones. Cyclizations of unsymmetrical derivatives mostly proceed with low regioselectivity. Exceptions are 3-aryl-3-silyloxy-2-en-1-ones prepared from aroylacetones, which usually react with very good regioselectivity. For example, dibenzo[*b*,*d*]pyran-6-ones have been prepared by [3+3] cyclizations of 3-aryl-3-silyloxy-2-en-1-ones and subsequent lactonization.[6] Recently, we have reported[7] a one-pot synthesis of 3-aryl-3,4-dihydroisocoumarins by domino[8] '[3+3] cyclization/lactonization' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-hex-4-en-3-ones. The regioselectivity of these reactions is controlled by chelation effects. Herein, we report full details and a comprehensive study of the scope.

2. Results and discussion

The reaction of the dianion of acetylacetone (**1**) with aldehydes **2a**–**h** afforded, following a known procedure,[9] condensation products **3a**–**h** (Scheme 1, Table 1). The NEt_3-mediated reaction of **3a**–**h** with Me_3SiCl resulted in chemoselective formation of 1-aryl-1-

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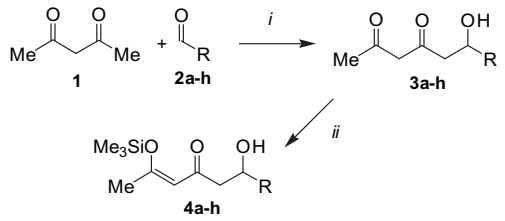


Scheme 1. Synthesis of 1-aryl-1-hydroxy-5-silyloxy-hex-4-en-3-ones **4a**–**h**: *i*: 1) **1**, 2.5 LDA, THF, 1 h, 0 °C; 2) **2a**–**h**, −78→20 °C, 14 h; 3) $NaHCO_3$, H_2O; *ii*: NEt_3, Me_3SiCl, CH_2Cl_2, 20 °C, 14 h.

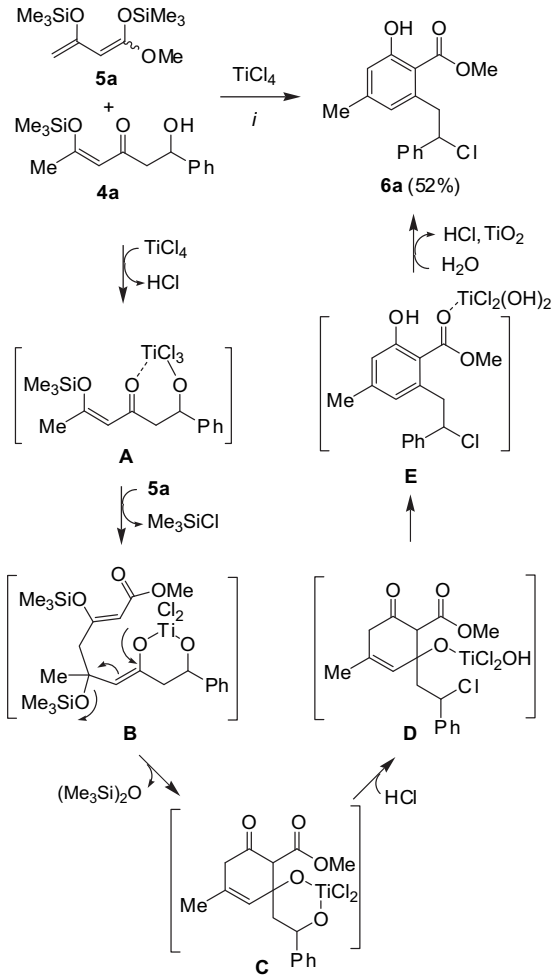
Table 1
Synthesis of 1-hydroxy-5-silyloxy-hex-4-en-3-ones **4a**–**h**

3,4	R	% (**3**)[a]	% (**4**)[a]
a	Ph	70	86
b	2-FC_6H_4	56	83
c	2,3-$(MeO)_2C_6H_3$	65	80
d	3-MeC_6H_4	63	90
e	4-MeC_6H_4	66	92
f	4-EtC_6H_4	74	95
g	4-ClC_6H_4	60	88
h	3-Pyridyl	45	78

[a] Yields of isolated products.

hydroxy-5-silyloxy-hex-4-en-3-ones **4a**–**h**. A silylation of the hydroxy group was not observed.

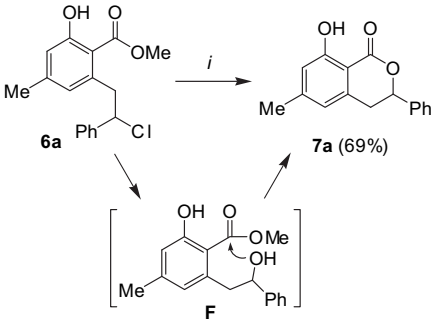
The $TiCl_4$-mediated [3+3] cyclization of 1-phenyl-1-hydroxy-5-silyloxy-hex-4-en-3-one **4a** with 1,3-bis(silyloxy)-1,3-butadiene **5a**, readily available from methyl acetoacetate, afforded 6-(2-phenyl-2-chloroethyl)salicylate **6a** (Scheme 2). The cyclization proceeded with excellent regioselectivity. The formation of the other regioisomer, 4-(2-phenyl-2-chloroethyl)salicylate, was not observed. The moderate yield of **6a** (52%) can be explained by practical problems during the chromatographic purification.



Scheme 2. Possible mechanism of the formation of **6a**: *i*: 1) $TiCl_4$, CH_2Cl_2, −78→20 °C, 14 h; 2) $NaHCO_3$, H_2O.

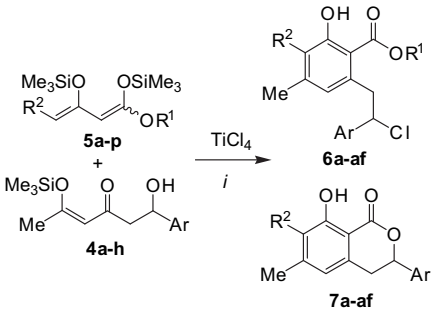
The regioselective formation of product **6a** might be explained by chelation-control. The reaction of $TiCl_4$ with **4a** gave intermediate **A** and hydrogen chloride. The chelation of Ti(IV) by the hydroxyl and the carbonyl group facilitates the conjugate addition of the (most reactive) terminal carbon atom of **5a** to **A** to give intermediate **B**, which underwent a cyclization to give intermediate **C**. The reaction of HCl with the carbon atom attached to the phenyl group resulted in nucleophilic substitution and formation of intermediate **D**, which underwent aromatization to give intermediate **E**. Product **6a** is formed upon aqueous work-up. Interestingly, the presence of the *free* hydroxy group of **4a** is important to achieve a high degree of regioselectivity. The presence of a methoxy rather than a hydroxyl group resulted in the formation of a mixture of regioisomers.

Stirring of a solution of **6a** in wet THF in the presence of silica gel afforded 3-phenyl-3,4-dihydroisocoumarin **7a** in 69% yield (Scheme 3). The formation of **7a** can be explained by acid-mediated hydrolysis of the chloride to give intermediate **F** and subsequent lactonisation.



Scheme 3. Synthesis of **7a**: *i*: SiO_2, wet THF, 14 h.

The [3+3] cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadiene **5b** afforded **6b**, which was transformed into lactone **7b** by stirring in the presence of wet silica gel for 14 h (Scheme 4, Table 2). The [3+3] cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadienes **5c**–**f**, containing an alkyl group attached to carbon atom C4, directly afforded the 3-phenyl-3,4-dihydroisocoumarins **7c**–**f**. The formation of **7b**–**d** can be explained by [3+3] cyclization and subsequent hydrolysis and lactonization during the aqueous work-up and/or silica gel chromatography. The cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadienes **5g**,**i**–**k** resulted in the formation of 6-(2-phenyl-2-chloroethyl)salicylates **6g**,**i**–**k**. The cyclization of various 1,3-bis(silyloxy)-1,3-butadienes with **4b**–**h**, containing phenyl groups with electron-withdrawing or -donating substituents, directly



Scheme 4. Synthesis of **6a**–**af** and **7a**–**af**: *i*: 1) $TiCl_4$, CH_2Cl_2, −78→20 °C, 14 h; 2) $NaHCO_3$, H_2O; 3) silica gel chromatography (EtOAc /heptanes).

Table 2
Synthesis of 6-(2-aryl-2-chloroethyl)salicylates **6a–af** and 3-aryl-3,4-dihydroisocoumarins **7a–af**

4	5	6,7	R^1	R^2	Ar	% (**6**)[a]	% (**7**)[a]
a	**a**	**a**	Me	H	Ph	52	69[b]
a	**b**	**b**	Me	Me	Ph	35	48[c]
a	**c**	**c**	Me	Et	Ph	0	33
a	**d**	**d**	Me	*n*Hex	Ph	0	57
a	**e**	**e**	Me	*n*Non	Ph	0	53
a	**f**	**f**	Me	*n*Dec	Ph	0	54
a	**g**	**g**	Me	Allyl	Ph	33	0
a	**h**	**h**	Me	$(CH_2)_2CH{=}CH_2$	Ph	0	42
a	**i**	**i**	Me	OMe	Ph	44	0
a	**j**	**j**	Et	H	Ph	37	0
a	**k**	**k**	^{i}Pr	H	Ph	40	0
b	**l**	**l**	Bn	H	2-FC_6H_4	0	50
b	**m**	**m**	Et	Me	2-FC_6H_4	0	46
c	**l**	**n**	Bn	H	2,3-$(MeO)_2C_6H_3$	0	38
c	**m**	**o**	Et	Me	2,3-$(MeO)_2C_6H_3$	0	35
d	**a**	**p**	Me	H	3-MeC_6H_4	0	42
d	**m**	**q**	Et	Me	3-MeC_6H_4	0	45
d	**c**	**r**	Me	Et	3-MeC_6H_4	0	54
d	**d**	**s**	Me	*n*Hex	3-MeC_6H_4	0	58
e	**a**	**t**	Me	H	4-MeC_6H_4	0	41
e	**b**	**u**	Me	Me	4-MeC_6H_4	0	43
e	**n**	**v**	Me	*n*Bu	4-MeC_6H_4	0	62
e	**g**	**w**	Me	Allyl	4-MeC_6H_4	0	35
e	**h**	**x**	Me	$(CH_2)_2CH{=}CH_2$	4-MeC_6H_4	0	38
e	**o**	**y**	Me	$(CH_2)_2Ph$	4-MeC_6H_4	0	40
f	**j**	**z**	Et	H	4-EtC_6H_4	0	48
g	**a**	**aa**	Me	H	4-ClC_6H_4	0	55
g	**b**	**ab**	Me	Me	4-ClC_6H_4	0	50
g	**c**	**ac**	Me	Et	4-ClC_6H_4	0	53
g	**d**	**ad**	Me	*n*Hex	4-ClC_6H_4	0	55
g	**p**	**ae**	Me	Cl	4-ClC_6H_4	28	0
h	**a**	**af**	Me	H	3-Pyridyl	0	37

[a] Yields of isolated products.
[b] Prepared from **6a**.
[c] Prepared from **6b**.

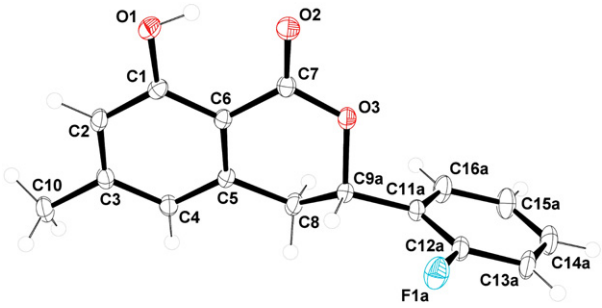


Figure 1. Ortep plot of **7l** (50% probability level); the position of the OH-proton was calculated from the difference map and refined freely.

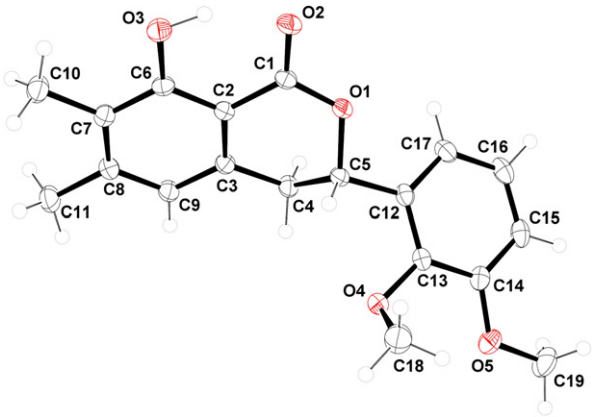


Figure 2. Ortep plot of **7o** (50% probability level); the position of the OH-proton was calculated from the difference map and refined freely.

afforded 3-aryl-3,4-dihydroisocoumarines **7l–af** (except for the reaction of **4g** with **5p** which gave **6ae**).

The silica gel chromatography generally proved to be important for the hydrolysis and lactonization to occur. In most reactions the direct formation of 2,3-dihydroisocoumarines was observed. The formation of products **6** mainly occurred when the phenyl-substituted silyl enol ether **4a** was employed. In this series, the choice of the 1,3-bis(silyloxy)-1,3-butadiene seems to have a significant influence on the product distribution. On the other hand, different products were obtained for reactions of one and the same 1,3-bis(silyloxy)-1,3-butadiene with different silyl enol ethers **4**. It was mentioned above that products **6** can be transformed into lactones **7** by stirring in the presence of wet silica gel. This result suggests that the quality and nature of the silica gel and of the solvent employed for the chromatographic purification also have an influence on the product distribution. In addition, the individual handling of each reaction may play a role. This includes, for example, the time required for the aqueous work-up or the preparation of the crude material for chromatography (concentration of a solution of the crude product in the presence of silica gel and addition of the solid residue on the top of the column or, alternatively, direct addition of the oily crude product by syringe without silica gel). In addition, the quality of the Lewis acid should have some influence (an older charge of $TiCl_4$ may be partly hydrolyzed and contains HCl).

The structures of all products were confirmed by spectroscopic methods. The structures of **7l**, **7o**, **7q** and **7af** were independently confirmed by X-ray crystal structure analyses (Figs. 1–4).[10]

The ethyl chloroformate-mediated reaction of 1,3-bis(silyl enol ether) **8**, readily available from acetylacetone, with imine **9** afforded condensation product **10**, which was transformed into silyl enol ether **11** (Scheme 5). The $TiCl_4$-mediated cyclization of **11** with **5a** and **5j** afforded products **12a** and **12b**, respectively. Products **12a** and **12b** were both formed as unseparable mixtures of regioisomers with a ratio of 0.49/0.51 and 0.47/0.53, respectively. Due to the rigid nature of the carbamate moiety, different rotamers are possible. For **12b**, the rotamers could be detected at low temperature (263 K). For one regioisomer, the ratio of the two rotamers was 0.53/0.47. For the other one the ratio was 0.62/0.38 (see Experimental section). The low regioselectivity might be explained by the fact that the amino group contains no free hydrogen atom.

In conclusion, we have reported a convenient synthesis of 3-aryl-3,4-dihydroisocoumarins by domino '[3+3] cyclization/lactonization' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones. These reactions proceed by regioselective [3+3] cyclization to give 6-(2-aryl-2-chloroethyl)salicylates and subsequent silica gel-mediated lactonization.

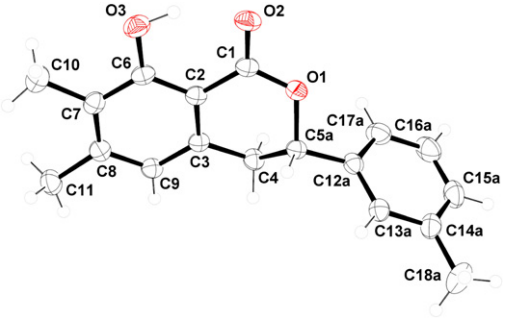


Figure 3. Ortep plot of **7q** (50% probability level); the position of the OH-proton was calculated from the difference map and refined freely.

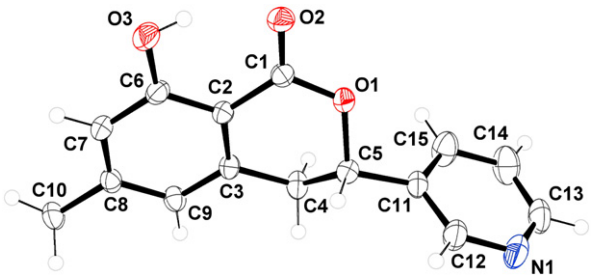
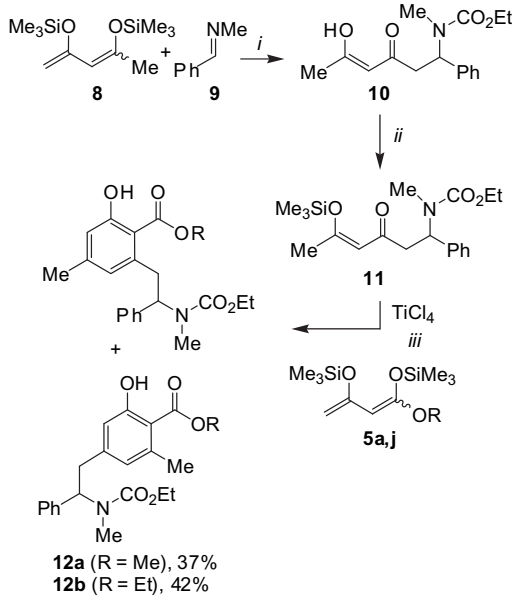


Figure 4. Ortep plot of **7af** (50% probability level); the position of the OH-proton was calculated from the difference map and refined freely.



Scheme 5. Synthesis of **12a**,**b**: *i*: 1) $ClCO_2Et$, CH_2Cl_2, 20 °C, 14 h, 2) EtOAc, cold H_2O; *ii*: NEt_3, Me_3SiCl, C_6H_6, 20 °C, 72 h; *iii*: 1) $TiCl_4$, CH_2Cl_2, −78→20 °C, 14 h; 2) $NaHCO_3$, H_2O.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

*3.1.1. General procedure for the synthesis of 1-hydroxy-2,4-benzodioates (**6a–af**) and 3-aryl-3,4-dihydroisocoumarins (**7c–af**).* To a CH_2Cl_2 solution (2 mL/1.0 mmol of **5**) of **5** (1.0 equiv) was added **4** (1.0 equiv) and subsequently $TiCl_4$ (1.0 equiv) at −78 °C under argon atmosphere. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the reaction mixture was added saturated aqueous $NaHCO_3$ solution (10 mL) and the organic and the aqueous layers were separated. The later was extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc=24/1) to give product **6** or **7**.

*3.1.2. Methyl-2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (**6a**).* Starting with 1,3-bis(silyl enol ether) **5a** (500 mg, 1.91 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (530 mg, 1.91 mmol) and $TiCl_4$ (0.21 mL, 1.91 mmol), **6a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a colourless oil (304 mg, 52%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.22 (s, 3H, CH_3), 3.61 (m, 2H, CH_2), 3.93 (s, 3H, OCH_3), 5.02 (m, 1H, CH), 6.41 (s, 1H, H_{Ar}), 6.72 (s, 1H, H_{Ar}), 7.29–7.35 (m, 5H, Ph), 11.23 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5 (CH_3), 46.7 (CH_2), 52.3 (OCH_3), 64.1 (CH), 109.5 (C_{Ar}), 117.3, 125.9, 126.9 ($2CH_{Ar}$), 128.3 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 139.4, 141.6, 145.3, 163.0 (C_{Ar}), 171.3 (C=O); IR (neat): $\tilde{\nu}$=2955 (w), 1653 (s), 1568 (m), 1452 (s), 1317 (s), 1261 (s), 1207 (s), 1092 (s), 955 (m), 855 (m), 728 (s), 691 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=306 (M^+, ^{37}Cl, 13), 304 (M^+, ^{35}Cl, 35), 268 (32), 237 (86), 208 (24), 179 (100), 165 (31), 125 (45), 119 (21), 89 (15), 77 (13); HRMS (EI): calcd for $C_{17}H_{17}ClO_3$ ([M]$^+$, [^{35}Cl]): 304.08715; found: 304.08607.

*3.1.3. Methyl 6-(2-chloro-2-phenylethyl)-2-hydroxy-3,4-dimethylbenzoate (**6b**).* Starting with 1,3-bis(silyl enol ether) **5b** (600 mg, 2.18 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (608 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a light yellow oil (243 mg, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.14 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.58 (m, 2H, CH_2), 3.93 (s, 3H, OCH_3), 5.01 (m, 1H, CH), 6.42 (s, 1H, H_{Ar}), 7.31–7.35 (m, 5H, Ph), 11.61 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 20.3 (CH_3), 46.7 (CH_2), 52.3 (OCH_3), 64.3 (CH), 108.7, 124.1 (C_{Ar}), 126.0 (CH_{Ar}), 126.9 ($2CH_{Ar}$), 128.5 ($3CH_{Ar}$), 136.0, 141.8, 143.4, 161.0 (C_{Ar}), 171.9 (C=O); IR (neat): $\tilde{\nu}$=2927 (m), 2862 (w), 1670 (s), 1629 (m), 1435 (w), 1220 (s), 1126 (m), 1041 (w), 970 (s), 901 (s), 810 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=320 (M^+, ^{37}Cl, 11), 318 (M^+, ^{35}Cl, 33), 282 (10), 251 (43), 250 (76), 222 (10), 194 (14), 193 (100), 179 (10), 178 (14), 161 (11), 133 (28), 125 (18), 91 (10), 77 (10); HRMS (EI): calcd for $C_{18}H_{19}ClO_3$ ([M]$^+$, [^{35}Cl]): 318.10172; found: 318.10196.

*3.1.4. Methyl-3-allyl-6-(2-chloro-2-phenylethyl)-2-hydroxy-4-methylbenzoate (**6g**).* Starting with 1,3-bis(silyl enol ether) **5g** (600 mg, 1.99 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)-hex-4-en-3-one **4a** (555 mg, 1.99 mmol) and $TiCl_4$ (0.21 mL, 1.99 mmol), **6g** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a slight yellow oil (226 mg, 33%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.04 (s, 3H, CH_3), 3.41 (d, 2H, *J*=2.5 Hz, CH_2), 3.57 (m, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.98–5.03 (m, 3H, CH,=CH_2), 5.91 (m, 1H, =CH), 6.43 (s, 1H, H_{Ar}), 7.24–7.34 (m, 5H, Ph), 11.59 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.4 (CH_3), 30.0, 46.5 (CH_2), 52.1 (OCH_3), 64.0 (CH), 108.8 (C_{Ar}), 114.3 (=CH_2), 125.2 (C_{Ar}), 126.1 (CH_{Ar}), 126.7 ($2CH_{Ar}$), 128.0 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 135.1 (=CH), 136.7, 141.5, 143.6, 160.7 (C_{Ar}), 171.6 (C=O); IR (neat): $\tilde{\nu}$=2920 (m), 2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s), 717 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=346 (M^+, ^{37}Cl, 15), 344 (M^+, ^{35}Cl, 43), 308 (26), 276 (67), 261 (39), 219 (100), 178 (15), 159 (22), 91 (23). Anal. Calcd (%) for $C_{20}H_{21}ClO_3$ (344.83): C 69.66, H 6.14; found: C 69.61, H 6.41.

*3.1.5. Methyl 6-(2-chloro-2-phenylethyl)-2-hydroxy-3-methoxy-4-methylbenzoate (**6i**).* Starting with 1,3-bis(silyl enol ether) **5i** (700 mg, 2.40 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (670 mg, 2.40 mmol) and $TiCl_4$ (0.26 mL, 2.40 mmol), **6i** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a slight yellow oil (350 mg, 44%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.07 (s, 3H, CH_3), 3.43 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.87 (m, 1H, CH), 6.28 (s, 1H, H_{Ar}), 7.12–7.21 (m, 5H, Ph), 11.24 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.0 (CH_3), 46.4 (CH_2), 52.4, 59.8 (OCH_3), 64.2 (CH), 110.5 (C_{Ar}), 125.9 (CH_{Ar}), 126.9 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 133.8, 137.2, 141.6, 145.7, 156.3 (C_{Ar}), 171.4 (C=O); IR (neat): $\tilde{\nu}$=2953 (w), 1658 (s), 1440 (m), 1309 (w), 1252 (s), 1199 (m), 1007 (m), 805 (w), 696 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z*

(%)=336 (M^+, ^{37}Cl, 2), 334 (M^+, ^{35}Cl, 6), 284 (59), 266 (100), 208 (27), 251 (20), 236 (30), 165 (23), 77 (20); HRMS (EI): calcd for $C_{18}H_{19}ClO_4$ ([M]$^+$, [^{35}Cl]): 334.09674; found: 334.09664.

*3.1.6. Ethyl-2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (**6j**).* Starting with 1,3-bis(silyl enol ether) **5j** (600 mg, 2.18 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (610 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **6j** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a slight yellow oil (257 mg, 37%). ^1H NMR (300 MHz, $CDCl_3$): δ=1.36 (t, 3H, J=7.1 Hz, CH_3), 2.15 (s, 3H, CH_3), 3.55 (dd, 1H, J=13.2, 6.8 Hz, CH_2), 3.75 (dd, 1H, J=13.2, 7.3 Hz, CH_2), 4.41 (q, 2H, J=7.1 Hz, OCH_2), 5.03 (dd, 1H, J=13.2, 7.0 Hz, CH), 6.27 (s, 1H, H_{Ar}), 6.68 (s, 1H, H_{Ar}), 7.27–7.30 (m, 5H, Ph), 11.45 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 21.3 (CH_3), 46.3 (CH_2), 61.8 (OCH_2), 63.7 (CH), 109.5 (C_{Ar}), 117.2 (CH_{Ar}), 125.7 (CH_{Ar}), 127.0 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 139.2, 141.2, 145.0, 163.0 (C_{Ar}), 170.9 (C=O); IR (neat): $\tilde{\nu}$=2980 (w), 1654 (s), 1620 (m), 1570 (w), 1452 (m), 1314 (s), 1258 (s), 1212 (s), 1095 (s), 1014 (w), 852 (w), 738 (m), 696 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=320 (M^+, ^{37}Cl, 9), 318 (M^+, ^{35}Cl, 27), 282 (28), 237 (79), 208 (27), 165 (100), 125 (29), 91 (12), 77 (10); HRMS (EI): calcd for $C_{18}H_{19}ClO_3$ ([M]$^+$, [^{35}Cl]): 318.10230; found: 318.10172.

*3.1.7. Isopropyl-2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (**6k**).* Starting with 1,3-bis(silyl enol ether) **5k** (600 mg, 2.07 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (576 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **6k** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as a slight yellow oil (275 mg, 40%). ^1H NMR (300 MHz, $CDCl_3$): δ=1.37 (d, 6H, J=6.3 Hz, $(CH_3)_2$), 2.11 (s, 3H, CH_3), 3.48 (dd, 1H, J=13.0, 7.5 Hz, CH_2), 3.87 (dd, 1H, J=13.0, 6.8 Hz, CH_2), 5.04 (dd, 1H, J=13.0, 6.8 Hz, CH), 5.32–5.40 (m, 1H, OCH), 6.16 (s, 1H, H_{Ar}), 6.66 (s, 1H, H_{Ar}), 7.24–7.30 (m, 5H, Ph), 11.45 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.3, 21.9 (CH_3), 46.1 (CH_2), 63.6 (CH), 70.1 (OCH), 109.5 (C_{Ar}), 117.2, 125.8 (CH_{Ar}), 127.3 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 139.1, 141.0, 144.8, 163.1 (C_{Ar}), 170.5 (C=O); IR (neat): $\tilde{\nu}$=2981 (w), 1650 (s), 1618 (m), 1571 (w), 1452 (m), 1367 (m), 1310 (m), 1259 (s), 1214 (s), 1090 (s), 1041 (w), 1090 (s), 909 (w), 852 (m), 738 (m), 695 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=334 (M^+, ^{37}Cl, 9), 332 (M^+, ^{35}Cl, 27), 296 (15), 254 (25), 237 (92), 208 (28), 179 (19), 165 (100), 125 (64), 91 (17); HRMS (EI): calcd for $C_{19}H_{21}ClO_3$ ([M]$^+$, [^{35}Cl]): 332.11759; found: 332.11734.

*3.1.8. Methyl-3-chloro-6-(2-chloro-2-(4-chlorophenyl)ethyl)-2-hydroxy-4-methylbenzoate (**6ae**).* Starting with 1,3-bis(silyl enol ether) **5p** (600 mg, 2.03 mmol), 1-(4-chlorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4g** (636 mg, 2.03 mmol) and $TiCl_4$ (0.22 mL, 2.03 mmol), **6ae** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=24/1) as an orange solid (212 mg, 28%), mp=135–137 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.25 (s, 3H, CH_3), 3.49 (m, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.89 (m, 1H, CH), 6.40 (s, 1H, H_{Ar}), 7.19 (d, 2H, J=8.5 Hz, $2H_{Ar}$), 7.25 (d, 2H, J=8.5 Hz, $2H_{Ar}$), 11.76 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.6 (CH_3), 46.4 (CH_2), 52.8 (OCH_3), 62.8 (CH), 110.4, 121.9 (C_{Ar}), 126.0 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 134.2, 136.8, 139.8, 143.1, 158.5 (C_{Ar}), 171.0 (C=O); IR (KBr): $\tilde{\nu}$=2953 (w), 2848 (w), 1728 (w), 1655 (s), 1607 (m), 1549 (m), 1492 (m), 1434 (s), 1391 (m), 1307 (m), 1263 (s), 1213 (s), 1091 (m), 1065 (m), 1013 (m), 956 (m), 870 (m), 804 (s), 769 (m), 722 (m), 651 (m), 579 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=376 (M^+, ^{37}Cl, 5), 374 (M^+, $^{37}Cl^{35}Cl$, 16), 372 (M^+, ^{35}Cl, 16), 338 (10), 336 (13), 307 (19), 306 (32), 305 (27), 304 (40), 215 (32), 214 (12), 213 (100), 178 (12), 161 (17), 159 (27), 153 (16); HRMS (EI): calcd for $C_{17}H_{15}Cl_3O_3$ ([M]$^+$, [^{35}Cl]): 372.00813; found: 372.00788.

*3.1.9. 7-Ethyl-8-hydroxy-6-methyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7c**).* Starting with 1,3-bis(silyl enol ether) **5c** (500 mg, 1.73 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (482 mg, 1.73 mmol) and $TiCl_4$ (0.19 mL, 1.73 mmol), **7c** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a white solid (161 mg, 33%), mp=116–117 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.4 Hz, CH_3), 2.33 (s, 3H, CH_3), 2.70 (q, 2H, J=7.4 Hz, CH_2), 3.02 (dd, 1H, J=16.4, 3.6 Hz, CH_2), 3.23 (dd, 1H, J=16.4, 12.0 Hz, CH_2), 5.53 (dd, 1H, J=12.0, 3.6 Hz, CH), 6.54 (s, 1H, H_{Ar}), 7.36–7.46 (m, 5H, Ph), 11.21 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.1 (CH_3), 19.0 (CH_2), 19.9 (CH_3), 35.0 (CH_2), 80.8 (CH), 105.8 (C_{Ar}), 119.6 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 128.3 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 129.7, 135.6, 138.2, 145.3, 160.1 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=3067 (w), 2964 (w), 2873 (w), 1660 (m), 1623 (m), 1571 (w), 1497 (m), 1415 (m), 1349 (m), 1281 (m), 1239 (s), 1162 (s), 1107 (m), 1029 (m), 976 (m), 917 (m), 854 (m), 801 (s), 754 (s), 693 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=282 (M^+, 61), 265 (21), 264 (100), 250 (10), 249 (53), 221 (10), 191 (8), 178 (19), 91 (8), 77 (12). Anal. Calcd (%) for $C_{18}H_{18}O_3$ (282.45): C 76.57, H 6.43; found: C 76.21, H 6.21.

*3.1.10. 7-Hexyl-8-hydroxy-6-methyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7d**).* Starting with 1,3-bis(silyl enol ether) **5d** (600 mg, 1.74 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (485 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **7d** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a colourless solid (336 mg, 57%), mp=69–71 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=0.70 (t, 3H, J=6.9 Hz, CH_3), 1.08–1.36 (m, 8H, $4CH_2$), 2.15 (s, 3H, CH_3), 2.48 (t, 2H, J=7.1 Hz, CH_2), 2.84 (dd, 1H, J=16.2, 3.4 Hz, CH_2), 3.05 (dd, 1H, J=16.3, 12.3 Hz, CH_2), 5.36 (dd, 1H, J=12.3, 3.4 Hz, CH), 6.36 (s, 1H, CH_{Ar}), 7.18–7.29 (m, 5H, Ph), 11.04 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.3, 21.3 (CH_3), 23.8, 27.0, 30.0, 30.7, 32.9, 36.2 (CH_2), 82.0 (CH), 106.9 (C_{Ar}), 120.7 (CH_{Ar}), 127.2 ($2CH_{Ar}$), 129.8 (C_{Ar}), 129.9 ($3CH_{Ar}$), 136.8, 139.4, 146.7, 161.5 (C_{Ar}), 171.4 (C=O); IR (KBr): $\tilde{\nu}$=3061 (w), 2921 (m), 2855 (m), 1658 (s), 1623 (s), 1573 (w), 1497 (w), 1450 (m), 1353 (m), 1243 (s), 1155 (s), 1085 (m), 1057 (m), 1013 (m), 927 (w), 860 (m), 804 (s), 751 (m), 699 (s), 604 (m), 537 (w) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=338 (M^+, 45), 320 (38), 321 (9), 305 (10), 291 (13), 251 (22), 250 (100), 249 (73), 179 (7), 178 (24); HRMS (EI): calcd for $C_{22}H_{26}O_3$ [M]$^+$: 338.18765; found: 338.18805.

*3.1.11. 8-Hydroxy-6-methyl-7-nonyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7e**).* Starting with 1,3-bis(silyl enol ether) **5e** (600 mg, 1.55 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (430 mg, 1.55 mmol) and $TiCl_4$ (0.17 mL, 1.55 mmol), **7e** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (311 mg, 53%), mp=142–144 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=0.81 (t, 3H, J=7.3 Hz, CH_3), 1.15–1.48 (m, 14H, $7CH_2$), 2.25 (s, 3H, CH_3), 2.58 (t, 2H, J=7.2 Hz, CH_2), 2.95 (dd, 1H, J=16.3, 3.4 Hz, CH_2), 3.17 (dd, 1H, J=16.3, 12.3 Hz, CH_2), 5.47 (dd, 1H, J=12.3, 3.4 Hz, CH), 6.47 (s, 1H, H_{Ar}), 7.28–7.39 (m, 5H, Ph), 11.14 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.0 20.1 (CH_3), 22.6, 25.8, 27.2, 28.8, 29.3, 29.5, 29.9, 31.8, 35.0 (CH_2), 80.8 (CH), 105.7 (C_{Ar}), 119.5 (CH_{Ar}), 126.0 ($2CH_{Ar}$), 128.6 (C_{Ar}), 128.7 ($3CH_{Ar}$), 135.5, 138.2, 145.5, 160.3 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=2921 (m), 2852 (m), 1659 (m), 1623 (m), 1573 (w), 1502 (w), 1450 (m), 1354 (m), 1269 (m), 1240 (s), 1155 (s), 1086 (m), 1029 (m), 915 (w), 843 (m), 804 (m), 751 (m), 699 (m), 609 (m), 538 (w) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=380 (M^+, 41), 363 (12), 362 (44), 291 (23), 251 (24), 250 (100), 249 (75), 178 (20); HRMS (EI): calcd for $C_{20}H_{20}O_3$ [M]$^+$: 380.23460; found: 330.23488.

*3.1.12. 7-Decyl-8-hydroxy-6-methyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7f**).* Starting with 1,3-bis(silyl enol ether) **5f** (700 mg, 1.74 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **4a** (485 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **7f** was isolated after column chromatography (silica gel, *n*-heptane/

EtOAc=23/2) as a colourless solid (372 mg, 54%), mp=127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=7.1 Hz, CH_3), 1.22–1.38 (m, 16H, 8CH_2), 2.32 (s, 3H, CH_3), 2.65 (t, 2H, J=8.2 Hz, CH_2), 3.02 (dd, 1H, J=16.5, 3.2 Hz, CH_2), 3.23 (dd, 1H, J=16.5, 12.3 Hz, CH_2), 5.54 (dd, 1H, J=12.3, 3.2 Hz, CH), 6.51 (s, 1H, H_{Ar}), 7.25–7.46 (m, 5H, Ph), 11.21 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 20.1 (CH_3), 22.6, 25.9, 27.3, 28.8, 29.3, 29.5, 29.6, 29.9, 31.8, 35.1 (CH_2), 80.8 (CH), 105.7 (C_{Ar}), 119.5 (CH_{Ar}), 126.0 (2CH_{Ar}), 128.5 (C_{Ar}), 128.6 (3CH_{Ar}), 135.5, 138.2, 145.5, 160.3 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=2920 (m), 2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s), 717 (s) cm^{-}; GC–MS (EI, 70 eV): m/z (%)=394 (M^+, 67), 306 (46), 291 (18), 264 (100), 249 (15), 192 (19), 91 (11); HRMS (EI): calcd for $C_{26}H_{34}O_3$ $[M]^+$: 394.17200; found: 394.17167.

*3.1.13. 7-(But-3-enyl)-8-hydroxy-6-methyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7h**).* Starting with 1,3-bis(silyl enol ether) **5h** (600 mg, 1.90 mmol), 1-hydroxy-1-phenyl-5-(trimethylsilyloxy)-hex-4-en-3-one **4a** (528 mg, 1.90 mmol) and $TiCl_4$ (0.20 mL, 1.90 mmol), **7h** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (251 mg, 43%), mp=86–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.20 (q, 2H, J=8.2 Hz, CH_2), 2.26 (s, 3H, CH_3), 2.69 (t, 2H, J=7.4, CH_2), 2.95 (dd, 1H, J=16.4, 3.2 Hz, CH_2), 3.17 (dd, 1H, J=16.4, 12.0 Hz, CH_2), 4.88–5.02 (m, 2H,=CH_2), 5.47 (dd, 1H, J=12.0, 3.2 Hz, CH), 5.78–5.90 (m, 1H, =CH), 6.48 (s, 1H, H_{Ar}), 7.26–7.40 (m, 5H, Ph), 11.16 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.2 (CH_3), 25.4, 32.8, 35.0 (CH_2), 80.8 (CH), 105.8 (C_{Ar}), 114.7 (=CH_2), 119.6 (CH_{Ar}), 126.1 (2CH_{Ar}), 127.4 (C_{Ar}), 128.7 (3CH_{Ar}), 135.9, 138.2 (C_{Ar}), 138.3 (=CH), 145.6, 160.4 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=3062 (w), 2940 (w), 1659 (s), 1622 (m), 1573 (m), 1537 (w), 1496 (m), 1415 (m), 1350 (m), 1287 (m), 1238 (s), 1162 (s), 1058 (m), 1006 (m), 908 (m), 843 (m), 800 (s), 755 (s), 697 (s), 586 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=308 (M^+, 19), 268 (6), 267 (28), 250 (19), 249 (100), 178 (13). Anal. Calcd (%) for $C_{20}H_{20}O_3$ (308.141): C 77.90, H 6.54; found: C 77.64, H 6.86; HRMS (EI): calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.14128; found: 308.14097.

*3.1.14. 3-(2-Fluorophenyl)-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7l**).* Starting with 1,3-bis(silyl enol ether) **5l** (600 mg, 1.78 mmol), 1-(2-fluorophenyl)-1-hydroxy-5-(trimethylsilyloxy)-hex-4-en-3-one **4b** (527 mg, 1.78 mmol) and $TiCl_4$ (0.19 mL, 1.78 mmol), **7l** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a colourless solid (241 mg, 50%), mp=144–146 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.27 (s, 3H, CH_3), 3.03 (dd, 1H, J=16.5, 4.0 Hz, CH_2), 3.16 (dd, 1H, J=16.5, 11.7 Hz, CH_2), 5.79 (dd, 1H, J=11.7, 4.0 Hz, CH), 6.49 (s, 1H, H_{Ar}), 6.67 (s, 1H, H_{Ar}), 6.98–7.06 (m, 1H, H_{Ar}), 7.11–7.17 (m, 1H, H_{Ar}), 7.24–7.33 (m, 1H, H_{Ar}), 7.48–7.55 (m, 1H, H_{Ar}), 10.78 (s, 1H, OH); ^{19}F-NMR (282 MHz, $CDCl_3$): δ=−118.7; ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (CH_3), 33.2 ($J_{F,C}$=1.5 Hz, CH_2), 73.9 ($J_{F,C}$=3.2 Hz, CH), 104.7 (C_{Ar}), 114.6 ($J_{F,C}$=21.1 Hz), 115.6, 118.2, 123.5 ($J_{F,C}$=3.6 Hz), (CH_{Ar}), 124.5 ($J_{F,C}$=12.4 Hz, C_{Ar}), 126.5 ($J_{F,C}$=3.2 Hz), 129.2 ($J_{F,C}$=8.3 Hz), (CH_{Ar}), 137.8, 147.1, 158.5 ($J_{F,C}$=247.5 Hz), 161.2 (C_{Ar}), 168.5 (C=O); IR (KBr): $\tilde{\nu}$=3073 (w), 2962 (w), 2909 (w), 1667 (s), 1630 (m), 1575 (m), 1492 (m), 1455 (m), 1366 (m), 1324 (m), 1273 (m), 1230 (s), 1205 (s), 1160 (m), 1088 (m), 1058 (s), 980 (m), 912 (m), 869 (m), 796 (s), 743 (s), 693 (s), 609 (m), 555 (w) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=273 (16), 272 (M^+, 91), 255 (17), 254 (100), 198 (12), 197 (25), 196 (10), 183 (33), 148 (25), 91 (18); HRMS (EI): calcd for $C_{16}H_{13}FO_3$ $[M]^+$: 272.08432; found: 272.08445. Anal. Calcd (%) for $C_{16}H_{13}FO_3$ (272.084): C 70.58, H 4.81; found: C 70.19, H 4.62.

*3.1.15. 3-(2-Fluorophenyl)-8-hydroxy-6,7-dimethyl-3,4-dihydro-isochroman-1-one (**7m**).* Starting with 1,3-bis(silyl enol ether) **5m** (600 mg, 2.07 mmol), 1-(2-fluorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4b** (613 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **7m** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a slight yellow solid (272 mg, 46%), mp=126–128 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.11 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.99 (dd, 1H, J=16.3, 3.8 Hz, CH_2), 3.13 (dd, 1H, J=16.3, 11.5 Hz, CH_2), 5.77 (dd, 1H, J=11.5, 3.8 Hz, CH), 6.49 (s, 1H, H_{Ar}), 6.97–7.05 (m, 1H, H_{Ar}), 7.11–7.17 (m, 1H, H_{Ar}), 7.23–7.32 (m, 1H, H_{Ar}), 7.49–7.56 (m, 1H, H_{Ar}), 11.11 (s, 1H, OH); ^{19}F-NMR (282 MHz, $CDCl_3$): δ=−118.8; ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.1, 20.7 (CH_3), 34.0 ($J_{F,C}$=1.0 Hz, CH_2), 75.1 ($J_{F,C}$=3.3 Hz, CH), 105.9 (C_{Ar}), 115.5 ($J_{F,C}$=21.5 Hz), 119.3 (CH_{Ar}), 123.6 (C_{Ar}), 124.5 ($J_{F,C}$=3.5 Hz, CH_{Ar}), 125.7 ($J_{F,C}$=12.5 Hz, C_{Ar}), 127.5 ($J_{F,C}$=3.1 Hz), 130.1 ($J_{F,C}$=8.7 Hz), (CH_{Ar}), 135.4, 146.2, 159.5 ($J_{F,C}$=247.3 Hz), 160.2 (C_{Ar}), 170.1 (C=O); IR (KBr): $\tilde{\nu}$=3049 (w), 2911 (w), 1650 (m), 1615 (m), 1573 (m), 1496 (m), 1451 (m), 1408 (m), 1351 (m), 1266 (m), 1240 (s), 1208 (m), 1152 (s), 1098 (s), 1034 (m), 915 (m), 831 (m), 795 (s), 744 (s), 680 (m), 607 (m), 542 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=286 (M^+, 58), 269 (18), 268 (100), 253 (19), 240 (18), 225 (14), 197 (19), 196 (14), 177 (7), 162 (9), 91 (10); HRMS (EI): calcd for $C_{17}H_{15}FO_3$ $[M]^+$: 286.09997; found: 286.10011. Anal. Calcd (%) for $C_{17}H_{15}FO_3$ (286.100): C 71.32, H 5.28; found: C 70.89, H 4.92.

*3.1.16. 3-(2,3-Dimethoxyphenyl)-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7n**).* Starting with 1,3-bis(silyl enol ether) **5l** (600 mg, 1.78 mmol), 1-(2,3-dimethoxyphenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4c** (602 mg, 1.78 mmol) and $TiCl_4$ (0.19 mL, 1.78 mmol), **7n** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (212 mg, 38%), mp=142–144 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.26 (s, 3H, CH_3), 2.96 (dd, 1H, J=16.4, 3.4 Hz, CH_2), 3.15 (dd, 1H, J=16.4, 11.9 Hz, CH_2), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.81 (dd, 1H, J=11.9, 3.4 Hz, CH), 6.47 (s, 1H, H_{Ar}), 6.66 (s, 1H, H_{Ar}), 6.82–6.89 (m, 1H, J=5.8, 3.8 Hz, H_{Ar}), 7.00–7.08 (d, 2H, J=5.8, 3.8 Hz, H_{Ar}), 10.87 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0 (CH_3), 34.5 (CH_2), 55.8, 61.0 (OCH_3), 76.2 (CH), 106.0 (C_{Ar}), 112.6, 116.4, 118.5, 119.1, 124.4 (CH_{Ar}), 131.9, 135.2, 139.5, 146.0, 152.5, 162.2 (C_{Ar}), 170.0 (C=O); IR (KBr): $\tilde{\nu}$=2939 (w), 2837 (w), 1714 (s), 1670 (m), 1627 (m), 1579 (m), 1482 (m), 1358 (m), 1313 (m), 1266 (m), 1231 (s), 1145 (s), 1086 (m), 1002 (m), 907 (w), 799 (m), 745 (m), 696 (s), 620 (w), 580 (m) cm^{-1}; MS (EI, 70 eV): m/z (%)=314 (M^+, 100), 296 (61), 281 (12), 268 (13), 253 (32), 225 (16), 165 (5), 148 (15) 91 (8). Anal. Calcd (%) for $C_{18}H_{18}O_5$ (314.11): C 68.78, H 5.77; found: C 68.51, H 6.02.

*3.1.17. 3-(2,3-Dimethoxyphenyl)-8-hydroxy-6,7-dimethyl-3,4-dihydro-isochroman-1-one (**7o**).* Starting with 1,3-bis(silyl enol ether) **5m** (600 mg, 2.07 mmol), 1-(2,3-dimethoxyphenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4c** (700 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **7o** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (237 mg, 35%), mp=141–142 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.11 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.94 (dd, 1H, J=16.4, 3.5 Hz, CH_2), 3.10 (dd, 1H, J=16.3, 12.0 Hz, CH_2), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.80 (dd, 1H, J=12.0, 3.5 Hz, CH), 6.47 (s, 1H, H_{Ar}), 6.82–6.89 (m, 1H, J=5.8, 3.8 Hz, H_{Ar}), 7.00–7.08 (d, 2H, J=5.8, 3.8 Hz, H_{Ar}), 11.20 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.0, 20.7 (CH_3), 34.3 (CH_2), 55.8, 61.0 (OCH_3), 76.3 (CH), 105.6 (C_{Ar}), 112.5, 118.5, 119.3 (CH_{Ar}), 123.4 (C_{Ar}), 124.4 (CH_{Ar}), 132.1, 136.0, 146.0, 152.4, 160.2 (C_{Ar}), 170.5 (C=O); IR (KBr): $\tilde{\nu}$=3008 (w), 2923 (w), 2829 (w), 1665 (s), 1627 (m), 1587 (m), 1481 (m), 1416 (m), 1274 (s), 1223 (m), 1158 (m), 1084 (s), 1004 (s), 940 (m), 867 (m), 797 (s), 747 (s), 657 (m), 602 (m), 547 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%)=328 (M^+, 91), 311 (20), 310 (100), 295 (25), 280 (9), 279 (19), 267 (18), 239 (8), 91 (10); HRMS (EI): calcd for $C_{19}H_{20}O_5$ $[M]^+$: 328.13053; found: 328.13083. Anal. Calcd (%) for $C_{19}H_{20}O_5$ (328.131): C 69.50, H 6.14; found: C 68.51, H 6.17.

*3.1.18. 8-Hydroxy-6-methyl-3-(m-tolyl)-3,4-dihydro-isochroman-1-one (**7p**).* Starting with 1,3-bis(silyl enol ether) **5a** (600 mg,

2.30 mmol), 1-hydroxy-1-(*m*-tolyl)-5-(trimethylsilyloxy)hex-4-en-3-one **4d** (672 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **7p** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (260 mg, 42%), mp=142–144 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.96 (dd, 1H, J=16.7, 3.4 Hz, CH_2), 3.18 (dd, 1H, J=16.7, 12.0 Hz, CH_2), 5.43 (dd, 1H, J=12.0, 3.4 Hz, CH), 6.47 (s, 1H, H_{Ar}), 6.66 (s, 1H, H_{Ar}), 7.09–7.25 (m, 4H, H_{Ar}), 10.84 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4, 22.0 (CH_3), 35.2 (CH_2), 80.8 (CH), 105.9 (C_{Ar}), 116.5, 119.1, 123.1, 126.7, 128.6, 129.5 (CH_{Ar}), 138.0, 138.5, 139.1, 147.9, 162.2 (C_{Ar}), 169.7 (C=O); IR (KBr): $\tilde{\nu}$=2921 (w), 1660 (m), 1631 (m), 1582 (s), 1486 (w), 1349 (m), 1274 (m), 1158 (m), 1092 (m), 976 (m), 847 (m), 698 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=268 (M^+, 100), 250 (60), 249 (18), 222 (75), 194 (10), 179 (33), 178 (22), 148 (27), 91 (29). Anal. Calcd (%) for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; found: C 75.98, H 6.32.

*3.1.19. 8-Hydroxy-6,7-dimethyl-3-(m-tolyl)-3,4-dihydro-isochroman-1-one (**7q**).* Starting with 1,3-bis(silyl enol ether) **5m** (600 mg, 2.07 mmol), 1-hydroxy-1-(*m*-tolyl)-5-(trimethylsilyloxy)-hex-4-en-3-one **4d** (605 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **7q** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (262 mg, 45%), mp=146–148 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.05 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.89 (dd, 1H, J=16.3, 3.3 Hz, CH_2), 3.11 (dd, 1H, J=16.3, 12.0 Hz, CH_2), 5.36 (dd, 1H, J=12.0, 3.3 Hz, CH), 6.42 (s, 1H, H_{Ar}), 7.03 (m, 4H, H_{Ar}), 11.12 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.0, 20.7, 21.4 (CH_3), 35.0 (CH_2), 80.9 (CH), 105.6 (C_{Ar}), 119.2, 123.1, 126.7, 128.5, 129.4 (CH_{Ar}), 135.6, 138.1, 138.4, 139.9, 146.0, 160.0 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=2918 (w), 2859 (w), 1659 (m), 1573 (m), 1445(m), 1349 (m), 1270 (m), 1197 (m), 1097 (m), 1019 (m), 955 (m), 861 (s), 800 (m), 758 (s), 712 (s), 610 (m), 564 (m) cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=282 (M^+, 75), 265 (20), 264 (100), 263 (18), 249 (45), 236 (30), 221 (14), 193 (15), 178 (15), 162 (9), 91 (16). Anal. Calcd (%) for $C_{18}H_{18}O_3$ (282.12): C 76.57, H 6.43; found: C 76.54, H 6.44.

*3.1.20. 7-Ethyl-8-hydroxy-6-methyl-3-(m-tolyl)-3,4-dihydro-isochroman-1-one (**7r**).* Starting with 1,3-bis(silyl enol ether) **5c** (600 mg, 2.07 mmol), 1-hydroxy-1-(*m*-tolyl)-5-(trimethylsilyloxy)-hex-4-en-3-one **4d** (605 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **7r** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (296 mg, 54%), mp=121–123 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.06 (t, 3H, J=7.5 Hz, CH_3), 2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.63 (q, 2H, J=7.5 Hz, CH_2), 2.93 (dd, 1H, J=16.4, 3.3 Hz, CH_2), 3.15 (dd, 1H, J=16.4, 12.4 Hz, CH_2), 5.42 (dd, 1H, J=12.4, 3.3 Hz, CH), 6.46 (s, 1H, H_{Ar}), 7.09–7.22 (m, 4H, H_{Ar}), 11.14 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.1 (CH_3), 19.0 (CH_2), 19.9, 21.4 (CH_3), 35.0 (CH_2), 80.9 (CH), 105.8 (C_{Ar}), 119.5, 123.1, 126.7, 128.5, 129.4 (CH_{Ar}), 129.7, 135.7, 138.2, 138.4, 145.2, 160.2 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=2963 (w), 2870 (w), 1660 (s), 1624 (m), 1572 (w), 1504 (w), 1442 (m), 1415 (m), 1349 (m), 1283 (m), 1238 (s), 1160 (s), 1107 (m), 1064 (m), 1033 (m), 977 (m), 912 (m), 858 (w), 805 (m), 755 (s), 706 (s), 611 (m), 573 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=296 (M^+, 60), 279 (21), 278 (100), 264 (11), 263 (56), 235 (9), 192 (9), 191 (9), 91 (8); HRMS (EI): calcd for $C_{19}H_{20}O_3$ $[M]^+$: 296.14070; found: 296.14101.

*3.1.21. 7-Hexyl-8-hydroxy-6-methyl-3-(m-tolyl)-3,4-dihydro-isochroman-1-one (**7s**).* Starting with 1,3-bis(silyl enol ether) **5d** (600 mg, 1.74 mmol), 1-hydroxy-1-(*m*-tolyl)-5-(trimethylsilyloxy)-hex-4-en-3-one **4d** (510 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **7s** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a slight yellow solid (356 mg, 58%), mp=71–73 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=0.72 (t, 3H, J=6.9 Hz, CH_3), 1.08–1.36 (m, 8H, $4CH_2$), 2.15 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.48 (t, 2H, J=6.2 Hz, CH_2), 2.83 (dd, 1H, J=16.2, 3.2 Hz, CH_2), 3.05 (dd, 1H, J=16.2, 12.4 Hz, CH_2), 5.33 (dd, 1H, J=12.4, 3.2 Hz, CH), 6.36 (s, 1H, H_{Ar}), 6.99–7.16 (m, 4H, H_{Ar}), 11.04 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.5, 21.3, 22.6 (CH_3), 23.8, 27.0, 30.0, 30.8, 32.9, 36.3 (CH_2), 82.1 (CH), 106.9 (C_{Ar}), 120.7, 124.2, 127.9, 129.6 (CH_{Ar}), 129.7 (C_{Ar}), 130.6 (CH_{Ar}), 136.9, 139.4, 139.6, 146.6, 161.5 (C_{Ar}), 171.5 (C=O); IR (KBr): $\tilde{\nu}$=2922 (m), 2855 (w), 1661 (s), 1622 (m), 1573 (w), 1512 (w), 1435 (m), 1354 (m), 1292 (m), 1244 (s), 1162 (s), 1078 (m), 1013 (m), 972 (w), 909 (w), 842 (m), 788 (s), 700 (m), 605 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=352 (M^+, 59), 335 (10), 334 (57), 319 (12), 265 (26), 264 (100), 263 (74), 249 (17), 192 (14), 191 (13); HRMS (EI): calcd for $C_{23}H_{28}O_3$ $[M]^+$: 352.20330; found: 352.20368.

*3.1.22. 8-Hydroxy-6-methyl-3-p-tolyl-3,4-dihydro-isochroman-1-one (**7t**).* Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), 1-hydroxy-1-(*p*-tolyl)-5-(trimethylsilyloxy)hex-4-en-3-one **4e** (672 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **7t** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a light yellow solid (252 mg, 41%), mp=111–113 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.34 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.04 (dd, 1H, J=16.4, 3.2 Hz, CH_2), 3.25 (dd, 1H, J=16.4, 12.2 Hz, CH_2), 5.51 (dd, 1H, J=12.2, 3.2 Hz, CH), 6.56 (s, 1H, H_{Ar}), 6.73 (s, 1H, H_{Ar}), 7.22 (d, 2H, J=8.0 Hz, H_{Ar}), 7.33 (d, 2H, J=8.0 Hz, H_{Ar}), 10.95 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.1, 22.0 (CH_3), 35.1 (CH_2), 80.7 (CH), 105.9 (C_{Ar}), 116.5, 119.1 (CH_{Ar}), 127.9 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1, 138.7, 139.1, 147.9, 162.2 (C_{Ar}), 169.8 (C=O); IR (KBr): $\tilde{\nu}$=2919 (w), 1660 (s), 1628 (s), 1578 (m), 1516 (w), 1349 (m), 1268 (m), 1230 (s), 1202 (s), 1157 (m), 1095 (s), 1058 (s), 975 (m), 854 (s), 814 (s), 732 (m), 695 (s) cm^{-1}; EIMS (EI, 70 eV): *m*/*z* (%)=268 (M^+, 100), 250 (75), 222 (78), 179 (23), 148 (17) 91 (15). Anal. Calcd (%) for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; found: C 75.98, H 6.32.

*3.1.23. 8-Hydroxy-6,7-dimethyl-3-(p-tolyl)-3,4-dihydro-isochroman-1-one (**7u**).* Starting with 1,3-bis(silyl enol ether) **5b** (600 mg, 2.18 mmol), 1-hydroxy-1-*p*-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **4e** (640 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **7u** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as an orange solid (265 mg, 43%), mp=107–109 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.16 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.99 (dd, 1H, J=16.1, 3.2 Hz, CH_2), 3.21 (dd, 1H, J=16.1, 12.1 Hz, CH_2), 5.49 (dd, 1H, J=12.1, 3.2 Hz, CH), 6.54 (s, 1H, H_{Ar}), 7.20 (d, 2H, J=7.9 Hz, H_{Ar}), 7.32 (d, 2H, J=7.9 Hz, H_{Ar}), 11.26 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.0, 20.7, 21.1 (CH_3), 34.8 (CH_2), 80.8 (CH), 105.6 (C_{Ar}), 119.2 (CH_{Ar}), 123.4 (C_{Ar}), 126.1 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 135.2, 135.6, 138.6, 146.0, 160.1 (C_{Ar}), 170.3 (C=O); IR (KBr): $\tilde{\nu}$=2920 (w), 1662 (s), 1575 (w), 1517 (m), 1449 (m), 1367 (m), 1276 (s), 1254 (s), 1160 (s), 1098 (m), 1017 (m), 965 (w), 859 (m), 809 (s), 750 (s), 695 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=282 (M^+, 65), 264 (100), 249 (34), 236 (24), 221 (15), 193 (16), 178 (20), 165 (8), 91 (21), 77 (9); HRMS (EI): calcd for $C_{18}H_{18}O_3$ $[M]^+$: 282.12505; found: 282.12562.

*3.1.24. 7-Butyl-8-hydroxy-6-methyl-3-(p-tolyl)-3,4-dihydro-isochroman-1-one (**7v**).* Starting with 1,3-bis(silyl enol ether) **5n** (700 mg, 2.21 mmol), 1-hydroxy-1-(*p*-tolyl)-5-(trimethylsilyloxy)hex-4-en-3-one **4e** (646 mg, 2.21 mmol) and $TiCl_4$ (0.24 mL, 2.21 mmol), **7v** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (444 mg, 62%), mp=83–84 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, 3H, J=7.1 Hz, CH_3), 1.36–1.47 (m, 4H, $2CH_2$), 2.30 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.63 (t, 2H, J=8.1 Hz, CH_2), 2.97 (dd, 1H, J=16.5, 3.2 Hz, CH_2), 3.20 (dd, 1H, J=16.5, 12.1 Hz, CH_2), 5.48 (dd, 1H, J=12.1, 3.2 Hz, CH), 6.51 (s, 1H, H_{Ar}), 7.26 (d, 2H, J=8.0 Hz, H_{Ar}), 7.31 (d, 2H, J=8.0 Hz, H_{Ar}), 11.21 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (CH_3), 20.1, 21.2 (CH_3), 23.0, 25.6, 31.0, 35.0 (CH_2), 80.8 (CH), 105.8 (C_{Ar}), 119.5 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 128.5 (C_{Ar}),

129.3 ($2CH_{Ar}$), 135.3, 135.7, 138.6, 145.5, 160.3 (C_{Ar}), 170.3 (C=O); IR (KBr): $\tilde{\nu}$=2920 (m), 2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s), 717 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=324 (M^+, 67), 306 (46), 291 (18), 264 (100), 249 (15), 192 (19), 91 (11); HRMS (EI): calcd for $C_{21}H_{24}O_3$ $[M]^+$: 324.17200; found: 324.17117.

*3.1.25. 7-Allyl-8-hydroxy-6-methyl-3-(p-tolyl)-3,4-dihydro-isochroman-1-one (**7w**).* Starting with 1,3-bis(silyl enol ether) **5g** (600 mg, 1.99 mmol), 1-hydroxy-1-(*p*-tolyl)-5-(trimethylsilyloxy)hex-4-en-3-one **4e** (582 mg, 1.99 mmol) and $TiCl_4$ (0.22 mL, 1.99 mmol), **7w** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (215 mg, 35%), mp=93–94 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.29 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.99 (dd, 1H, *J*=16.6, 3.3 Hz, CH_2), 3.21 (dd, 1H, *J*=16.6, 12.0 Hz, CH_2), 3.42 (d, 2H, *J*=5.9 Hz, CH_2), 4.81–5.11 (m, 2H, CH_2), 5.49 (dd, 1H, *J*=12.0, 3.3 Hz, CH), 5.84–5.97 (m, 1H, CH), 6.54 (s, 1H, H_{Ar}), 7.19 (d, 2H, *J*=8.1 Hz, H_{Ar}), 7.31 (d, 2H, *J*=8.1 Hz, H_{Ar}), 11.25 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.1, 21.2 (CH_3), 29.8, 34.9 (CH_2), 80.8 (CH), 105.9 (C_{Ar}), 114.8 (=CH_2), 119.6 (CH_{Ar}), 123.3 (C_{Ar}), 125.0 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 135.1 (=CH), 135.2, 136.5, 138.6, 146.3, 160.1 (C_{Ar}), 170.2 (C=O); IR (KBr): $\tilde{\nu}$=3061 (w), 2904 (w), 1659 (s), 1432 (m), 1352 (m), 1271 (s), 1239 (s), 1153 (s), 1070 (m), 1008 (m), 912 (m), 824 (s) 756 (s), 720 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=308 (M^+, 100), 290 (82), 275 (86), 247 (28), 203 (19), 173 (14), 115 (21), 91 (22); HRMS (EI): calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.14070; found: 308.14130.

*3.1.26. 7-(But-3-enyl)-8-hydroxy-6-methyl-3-(p-tolyl)-3,4-dihydro-isochroman-1-one (**7x**).* Starting with 1,3-bis(silyl enol ether) **5h** (600 mg, 1.90 mmol), 1-hydroxy-1-*p*-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **4e** (555 mg, 1.90 mmol) and $TiCl_4$ (0.20 mL, 1.90 mmol), **7x** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a light orange solid (234 mg, 38%), mp=98–99 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.75 (t, 2H, *J*=7.7 Hz, CH_2), 2.96 (dd, 1H, *J*=16.6, 3.3 Hz, CH_2), 3.19 (dd, 1H, *J*=16.6, 12.2 Hz, CH_2), 4.95–5.07 (m, 2H, CH_2), 5.46 (dd, 1H, *J*=12.2, 3.3 Hz, CH_2), 5.85–5.96 (m, 1H, =CH), 6.53 (s, 1H, H_{Ar}), 7.20 (d, 2H, *J*=8.0 Hz, H_{Ar}), 7.31 (d, 2H, *J*=8.0 Hz, H_{Ar}), 11.25 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.3, 21.2 (CH_3), 26.0, 32.8, 35.0 (CH_2), 80.9 (CH–O), 105.9 (C_{Ar}), 114.6 (=CH_2), 119.6 (CH_{Ar}), 126.5 ($2CH_{Ar}$), 127.4 (C_{Ar}), 129.4 ($2CH_{Ar}$), 135.3, 136.1 (C_{Ar}), 138.4 (=CH), 138.6, 145.6, 160.4 (C_{Ar}), 170.3 (C=O); IR (KBr): $\tilde{\nu}$=3079 (w), 2953 (w), 1656 (s), 1573 (w), 1514 (m), 1444 (m), 1350 (m), 1241 (s), 1158 (s), 1072 (m), 1017 (m), 906 (m), 815 (s), 745 (s), 652 (w), 599 (m), 526 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=322 (M^+, 19), 304 (3), 281 (15), 264 (19), 263 (100), 192 (9), 191 (7), 91 (4), 77 (2); HRMS (EI): calcd for $C_{21}H_{22}O_3$ $[M^+]$: 322.15635; found: 322.15602.

*3.1.27. 8-Hydroxy-6-methyl-7-phenethyl-3-(p-tolyl)-3,4-dihydro-isochroman-1-one (**7y**).* Starting with 1,3-bis(silyl enol ether) **5o** (600 mg, 1.64 mmol), 1-hydroxy-1-*p*-tolyl-5-(trimethylsilyloxy)-hex-4-en-3-one **4e** (480 mg, 1.64 mmol) and $TiCl_4$ (0.18 mL, 1.64 mmol), **7y** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a colourless solid (245 mg, 40%), mp=151–152 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.19 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.81 (t, 2H, *J*=4.5 Hz, CH_2), 2.93 (t, 2H, *J*=4.5 Hz, CH_2), 2.99 (dd, 1H, *J*=16.6, 3.2 Hz, CH_2), 3.22 (dd, IH, *J*=16.6, 12.2 Hz, CH_2), 5.49 (dd, 1H, *J*=12.2, 3.2 Hz CH), 6.51 (s, 1H, H_{Ar}), 7.19–7.34 (m, 9H, H_{Ar}), 11.30 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.1, 21.2 (CH_3), 28.4, 34.9, 35.0 (CH_2), 80.8 (CH), 105.9 (C_{Ar}), 119.6, 125.9 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 127.3 (C_{Ar}), 128.3 ($2CH_{Ar}$), 128.5 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 135.3, 136.2, 138.7, 142.2, 145.7, 160.4 (C_{Ar}), 170.3 (C=O); IR (KBr): $\tilde{\nu}$=3027 (w), 2953 (w), 1663 (s), 1573 (w), 1516 (m), 1449 (m), 1361 (m), 1288 (s), 1247 (s), 1160 (s), 1081 (m), 1016 (m), 968 (w), 918 (w), 858 (m), 751 (s), 694 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=372 (M^+, 20), 281 (20), 264 (19), 263 (100), 192 (9),191 (7), 91 (11), 77 (3). Anal. Calcd (%) for $C_{25}H_{26}O_3$ (372.17): C 80.80, H 6.78; found: C 80.72, H 6.53.

*3.1.28. 3-(4-Ethylphenyl)-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7z**).* Starting with 1,3-bis(silyl enol ether) **5j** (600 mg, 2.18 mmol), 1-(4-ethylphenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4f** (668 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **7z** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a yellow solid (295 mg, 48%), mp=103–104 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.24 (t, 3H, *J*=7.6 Hz, CH_3), 2.34 (s, 3H, CH_3), 2.67 (q, 2H, *J*=7.6 Hz, CH_2), 3.04 (dd, 1H, *J*=16.6, 3.2 Hz, CH_2), 3.21 (dd, 1H, *J*=16.6, 12.1 Hz, CH_2), 5.51 (dd, 1H, *J*=12.1, 3.2 Hz, CH), 6.55 (s, 1H, H_{Ar}), 6.73 (s, 1H, H_{Ar}), 7.21 (d, 2H, *J*=8.1 Hz, H_{Ar}), 7.36 (d, 2H, *J*=8.1 Hz, H_{Ar}), 10.93 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.5, 22.1 (CH_3), 28.6, 35.1 (CH_2), 80.7 (CH), 106.0 (C_{Ar}), 116.5, 119.1 (CH_{Ar}), 126.2 ($2CH_{Ar}$), 128.2 ($2CH_{Ar}$), 135.3, 139.1, 145.1, 147.9, 162.2 (C_{Ar}), 169.8 (C=O); IR (KBr): $\tilde{\nu}$=2966 (w), 1660 (s), 1576 (m), 1497 (w), 1347 (m), 1279 (m), 1201 (s), 1058 (s), 1008 (w), 913 (w), 829 (s), 769 (w), 700 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=282 (M^+, 100), 265 (15), 264 (92), 236 (28), 221 (62), 178 (11) 148 (17), 91 (10), 77 (4). Anal. Calcd (%) for $C_{18}H_{18}O_3$ (282.45): C 76.57, H 6.43; found: C 76.46, H 6.12.

*3.1.29. 3-(4-Chlorophenyl)-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7aa**).* Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), 1-(4-chlorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4g** (720 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **7aa** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a colourless solid (365 mg, 55%), mp=115–116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.34 (s, 3H, CH_3), 3.04 (dd, 1H, *J*=16.4, 3.6 Hz, CH_2), 3.21 (dd, 1H, *J*=16.4, 11.8 Hz, CH_2), 5.53 (dd, 1H, *J*=11.8, 3.6 Hz, CH), 6.56 (s, 1H, H_{Ar}), 6.74 (s, 1H, H_{Ar}), 7.38–7.40 (m, 4H, H_{Ar}), 10.85 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0 (CH_3), 35.1 (CH_2), 79.8 (CH), 105.8 (C_{Ar}), 116.7, 119.1 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 134.6, 136.6, 138.6, 148.2, 162.2 (C_{Ar}), 169.4 (C=O); IR (KBr): $\tilde{\nu}$=3070 (w), 2959 (w), 1673 (s), 1577 (m), 1491 (m), 1409 (m), 1360 (m), 1276 (m), 1229 (s), 1160 (m), 1085 (s), 1010 (m), 968 (w), 914 (m), 839 (s), 797 (s), 730 (s), 692 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=290 (M^+, ^{37}Cl, 26), 288 (M^+, ^{35}Cl, 87), 270 (100), 242 (45), 207 (21), 179 (39), 148 (26), 91 (12); HRMS (EI): calcd for $C_{16}H_{13}ClO_3$ ($[M]^+$, $[^{35}Cl]$): 288.06442; found: 288.064851.

*3.1.30. 3-(4-Chlorophenyl)-8-hydroxy-6,7-dimethyl-3,4-dihydro-isochroman-1-one (**7ab**).* Starting with 1,3-bis(silyl enol ether) **5b** (500 mg, 1.82 mmol), 1-(4-chlorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4g** (570 mg, 1.82 mmol) and $TiCl_4$ (0.20 mL, 1.82 mmol), **7ab** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a white solid (275 mg, 50%), mp=125–126 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=2.17 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.04 (dd, 1H, *J*=16.3, 3.5 Hz, CH_2), 3.18 (dd, 1H, *J*=16.3, 11.8 Hz, CH_2), 5.51 (dd, 1H, *J*=11.8, 3.5 Hz, CH), 6.55 (s, 1H, H_{Ar}), 7.37–7.39 (m, 4H, H_{Ar}), 11.18 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.1, 20.7 (CH_3), 34.9 (CH_2), 80.0 (CH), 105.4 (C_{Ar}), 119.3 (CH_{Ar}), 123.7 (C_{Ar}), 127.4 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 134.5, 135.1, 136.7, 146.2, 160.2 (C_{Ar}), 169.9 (C=O); IR (KBr): $\tilde{\nu}$=3152 (w), 2920 (w), 1651 (s), 1623 (m), 1574 (w), 1491 (m), 1354 (m), 1273 (m), 1215 (m), 1160 (s), 1074 (s), 964 (m), 872 (m), 815 (s), 718 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=304 (M^+, ^{37}Cl, 17), 302 (M^+, ^{35}Cl, 52), 284 (100), 269 (17), 256 (15), 249 (26), 241 (11), 193 (12), 178 (24), 165 (8), 91 (13), 77 (12); HRMS (EI): calcd for $C_{17}H_{15}ClO_3$ ($[M]^+$, $[^{35}Cl]$): 302.07042; found: 302.070344.

*3.1.31. 3-(4-Chlorophenyl)-7-ethyl-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7ac**).* Starting with 1,3-bis(silyl enol ether)

5c (600 mg, 2.07 mmol), 1-(4-chlorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4g** (648 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **7ac** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a brownish solid (347 mg, 53%), mp=110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (t, 3H, *J*=7.4 Hz, CH_3), 2.26 (s, 3H, CH_3), 2.63 (q, 2H, *J*=7.4 Hz, CH_2), 2.94 (dd, 1H, *J*=16.4, 3.2 Hz, CH_2), 3.11 (dd, 1H, *J*=16.4, 12.0 Hz, CH_2), 5.44 (dd, 1H, *J*=12.0, 3.2 Hz, CH), 6.47 (s, 1H, H_{Ar}), 7.31–7.33 (m, 4H, H_{Ar}), 11.07 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.0 (CH_3), 18.0 (CH_2), 18.9 (CH_3), 33.9 (CH_2), 79.0 (CH), 104.6 (C_{Ar}), 118.6 (CH_{Ar}), 126.4 ($2CH_{Ar}$), 127.9 ($2CH_{Ar}$), 128.9, 133.5, 134.2, 135.7, 144.4, 159.2 (C_{Ar}), 168.9 (C=O); IR (KBr): $\tilde{\nu}$=2930 (m), 2871 (w), 1658 (s), 1620 (m), 1493 (m), 1417 (m), 1359 (m), 1274 (m), 1236 (s), 1151 (s), 1062 (m), 1012 (m), 917 (m), 802 (s), 747 (s), 682 (m), 606 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=318 (M^+, ^{37}Cl, 15), 316 (M^+, ^{35}Cl, 49), 300 (34), 299 (22), 298 (100), 285 (14), 283 (44), 191 (11), 91 (11); HRMS (EI): calcd for $C_{18}H_{17}ClO_3$ ([M]$^+$, [^{35}Cl]): 316.08607; found: 316.08635.

*3.1.32. 3-(4-Chlorophenyl)-7-hexyl-8-hydroxy-6-methyl-3,4-dihydro-isochroman-1-one (**7ad**).* Starting with 1,3-bis(silyl enol ether) **5d** (600 mg, 1.74 mmol), 1-(4-chlorophenyl)-1-hydroxy-5-(trimethylsilyloxy)hex-4-en-3-one **4g** (545 mg, 1.74 mmol) and $TiCl_4$ (0.19 mL, 1.74 mmol), **7ad** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a viscous orange oil (357 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.72 (t, 3H, *J*=6.9 Hz, CH_3), 1.08–1.35 (m, 8H, $4CH_2$), 2.15 (s, 3H, CH_3), 2.48 (t, 2H, *J*=7.1 Hz, CH_2), 2.84 (dd, 1H, *J*=16.2, 3.4, CH_2), 3.01 (dd, 1H, *J*=16.2, 12.0 Hz, CH_2), 5.34 (dd, 1H, *J*=12.0, 3.4 Hz, CH), 6.36 (s, 1H, H_{Ar}), 7.20–7.22 (m, 4H, H_{Ar}), 10.97 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=15.2, 21.3 (CH_3), 23.8, 27.0, 29.9, 30.7, 32.9, 36.2 (CH_2), 81.2 (CH), 106.8 (C_{Ar}), 120.7 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 129.9 (C_{Ar}), 130.1 ($2CH_{Ar}$), 135.7, 136.4, 138.0, 146.9, 161.6 (C_{Ar}), 171.1 (C=O); IR (neat): $\tilde{\nu}$=3197 (w), 2924 (m), 2853 (m), 1934 (w), 1747 (w), 1662 (s), 1620 (m), 1573 (w), 1492 (m), 1434 (m), 1346 (m), 1272 (m), 1156 (s), 1073 (m), 1010 (s), 874 (w), 818 (s), 747 (m), 639 (m), 539 (m) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=374 (M^+, ^{37}Cl, 8), 372 (M^+, ^{35}Cl, 43), 356 (14), 354 (41), 339 (12), 325 (11), 286 (35), 285 (42), 284 (100), 283 (63), 249 (8), 192 (13), 191 (15), 177 (8); HRMS (EI): calcd for $C_{22}H_{25}ClO_3$ ([M]$^+$, [^{35}Cl]): 372.89523; found: 372.63828.

*3.1.33. 8-Hydroxy-6-methyl-3-(pyrid-4-yl)-3,4-dihydro-isochroman-1-one (**7af**).* Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), 1-hydroxy-1-(pyridin-3-yl)-5-(trimethylsilyloxy)hex-4-en-3-one **4h** (643 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **7af** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a slight yellow solid (216 mg, 37%), mp=124–126 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.28 (s, 3H, CH_3), 3.02 (dd, 1H, *J*=16.6, 3.8 Hz, CH_2), 3.20 (dd, 1H, *J*=16.6, 12.2 Hz, CH_2), 5.54 (dd, 1H, *J*=12.2, 3.8 Hz, CH), 6.51 (s, 1H, H_{Ar}), 6.68 (s, 1H, H_{Ar}), 7.30 (dd (br), 1H, *J*=7.9, 4.9 Hz, H_{Pyrid}), 7.77 (dt (br), 1H, *J*=7.9, 1.9 Hz, H_{Pyrid}), 8.56 (dd (br), 1H, *J*=4.9, 1.6 Hz, H_{Pyrid}), 8.61 (d (br), 1H, *J*=1.6 Hz, H_{Pyrid}), 10.73 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0 (CH_3), 34.8 (CH_2), 78.3 (CH), 105.7 (C_{Ar}), 116.8, 119.2 (CH_{Ar}), 123.7 (CH_{Pyrid}), 133.8 (C_{Ar}), 133.9 (CH_{Pyrid}), 138.3 (C_{Pyrid}), 147.6 (CH_{Pyrid}), 148.3 (C_{Ar}), 150.1 (CH_{Pyrid}), 162.3 (C_{Ar}), 169.2 (C=O); IR (KBr): $\tilde{\nu}$=3145 (br w), 2919 (w), 1659 (s), 1578 (m), 1495 (m), 1417 (m), 1349 (m), 1269 (s), 1202 (s), 1157 (m), 1096 (m), 975 (m), 886 (m), 814 (s), 781 (m), 695 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=255 (M^+, 100), 210 (93), 180 (73), 148 (52), 91 (17), 77 (6). Anal. Calcd (%) for $C_{15}H_{13}NO_3$ (255.09): C 70.58, H 5.13, N 5.49; found: C 69.53, H 5.32, N 5.02.

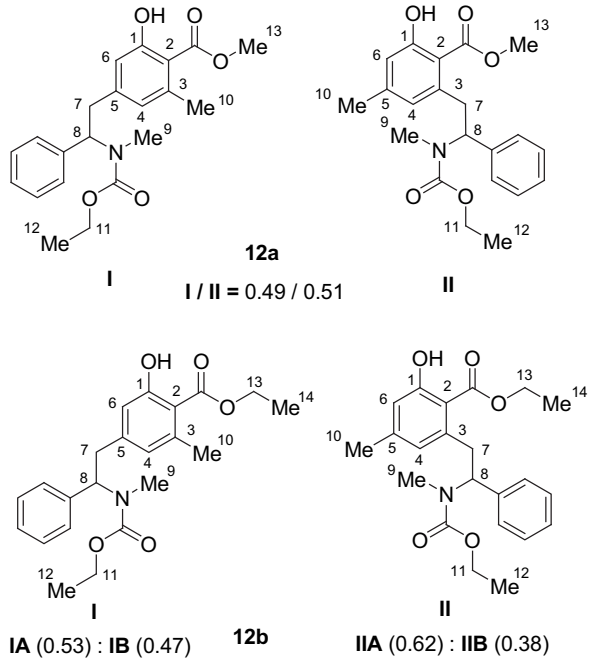
*3.1.34. Typical procedure for the synthesis of 3-aryl-3,4-dihydroisocoumarins **7a**,**b** from **6a**,**b**.* To a THF solution of **6a**,**b** (0.62 mmol) silica gel (Merck silica gel 60, 0.063–0.200 mm, 70–230 mesh, 1.5 g) was added and the mixture was stirred at room temperature for 6–14 h. After completion of the reaction (TLC control), THF was removed in vacuo. The residue was purified by chromatography (silica gel, heptane/ethyl acetate=23/2) to give **7**.

*3.1.35. 8-Hydroxy-6-methyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7a**).* Starting with **6a** (190 mg, 0.62 mmol) and silica gel (Merck silica gel 60, 0.063–0.200 mm, 70–230 mesh, 1.5 g), **7a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a white solid (110 mg, 69%), mp=125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.34 (s, 3H, CH_3), 3.07 (dd, 1H, *J*=16.5, 3.3 Hz, CH_2), 3.27 (dd, 1H, *J*=16.5, 12.0 Hz, CH_2), 5.56 (dd, 1H, *J*=12.0, 3.3 Hz, CH), 6.56 (s, 1H, H_{Ar}), 6.74 (s, 1H, H_{Ar}), 7.39–7.45 (m, 5H, Ph), 10.92 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0 (CH_3), 35.2 (CH_2), 80.7 (CH), 105.9 (C_{Ar}), 116.5, 119.1 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 128.7 (CH_{Ar}), 128.8 ($2CH_{Ar}$), 138.0, 139.0, 148.1, 162.2 (C_{Ar}), 169.7 (C=O); IR (KBr): $\tilde{\nu}$=3089 (w), 1652 (s), 1455 (m), 1277 (m), 1097 (s), 1060 (s), 912 (w), 845 (s), 798 (s), 699 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=254 (M^+, 100), 236 (69), 208 (61), 179 (40), 165 (51), 148 (31), 91 (28), 77 (22). Anal. Calcd (%) for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55; found: C 75.11, H 5.56.

*3.1.36. 8-Hydroxy-6,7-dimethyl-3-phenyl-3,4-dihydro-isochroman-1-one (**7b**).* Starting with **6b** (160 mg, 0.50 mmol) and silica gel (Merck silica gel 60, 0.063–0.200 mm, 70–230 mesh, 1.5 g), **7b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a light yellow solid (65 mg, 48%), mp=99–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.04 (dd, 1H, *J*=16.3, 3.4 Hz, CH_2), 3.24 (dd, 1H, *J*=16.3, 12.2 Hz, CH_2), 5.54 (dd, 1H, *J*=12.2, 3.4 Hz, CH), 6.56 (s, 1H, H_{Ar}), 7.37–7.43 (m, 5H, H_{Ar}), 11.23 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 20.7 (CH_3), 35.0 (CH_2), 80.9 (CH), 104.4 (C_{Ar}), 119.2 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 129.4, 136.7, 142.2, 145.4, 160.3 (C_{Ar}), 168.9 (C=O); IR (KBr): $\tilde{\nu}$=2919 (w), 1657 (s), 1573 (m), 1510 (w), 1356 (m), 1272 (m), 1226 (s), 1165 (m), 1097 (s), 1059 (s), 973 (m), 849 (s), 810 (s), 697 (s) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%)=268 (M^+, 60), 250 (100), 222 (28), 179 (23), 91 (21), 77 (14). Anal. Calcd (%) for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; found: C 75.81, H 6.22.

*3.1.37. Methyl-4-(2-(ethoxycarbonyl(methyl)amino)-2-phenylethyl)-2-hydroxy-6-methylbenzoate and methyl-2-(2-(ethoxycarbonyl(methyl)amino)-2-phenylethyl)-6-hydroxy-4-methylbenzoate (**12a**).* Starting with 1,3-bis(silyl enol ether) **5a** (600 mg, 2.30 mmol), ethyl methyl(3-oxo-1-phenyl-5-(trimethylsilyloxy)hex-4-enyl)carbamate **11** (835 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **12a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a slight orange oil (316 mg, 37%) a two different regioisomers in a ratio of 0.51 (II):0.49 (I). ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ=0.93–1.12 (br, $3H_{(II)}$, $H\text{-}12_{(II)}$); 1.16 (t, ^3J=7.3 Hz, $3H_{(I)}$, $H\text{-}12_{(I)}$); 2.25 (s, $3H_{(II)}$, $H\text{-}10_{(II)}$); 2.49 (s, $3H_{(I)}$, $H\text{-}10_{(I)}$); 2.63 (s, $3H_{(I)}$, $3H_{(II)}$, $H\text{-}9_{(I,II)}$); 3.03–3.11 (m), 3.20 (dd, ^2J=14.2 Hz, ^3J=5.7 Hz), ($2H_{(I)}$ or $H_{(II)}$, $1H_{(I)}$ or $H_{(II)}$, $H\text{-}7_{(I)}$, $H\text{-}7_{(II)}$); 3.78 (s, $3H_{(II)}$, $H\text{-}13_{(II)}$); 3.91 (s, $3H_{(I)}$, $H\text{-}13_{(I)}$); 3.86 (br), 4.04 (br), ($2H_{(I)}$, $2H_{(II)}$, $1H_{(I)}$ or $H_{(II)}$, $H\text{-}11_{(I)}$, $H\text{-}11_{(II)}$, $H\text{-}7_{(I)}$ or $H\text{-}7_{(II)}$); 5.50–5.76 (br, $1H_{(I)}$, $1H_{(II)}$, $H\text{-}8_{(I,II)}$); 6.45 (d, ^4J=1.5 Hz), 6.61 (br), ($1H_{(I)}$, $1H_{(II)}$, $H\text{-}4_{(I,II)}$); 6.69 (br), 6.71 (d, ^4J=1.5 Hz), ($1H_{(I)}$, $1H_{(II)}$, $H\text{-}6_{(I,II)}$); 7.25–7.38 (br, $5H_{(I)}$, $5H_{(II)}$, $Ph_{(I,II)}$); 11.28 (s, $1H_{(II)}$, $OH_{(II)}$); ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ=14.1, 14.5 ($C\text{-}12_{(I,II)}$); 21.5 ($C\text{-}10_{(II)}$); 24.0 ($C\text{-}10_{(I)}$); 28.8, 29.2 (br) ($C\text{-}9_{(I,II)}$); 36.4, 36.7 ($C\text{-}7_{(I,II)}$); 51.9, 52.1 ($C\text{-}13_{(I,II)}$); 58.0, 58.9 ($C\text{-}8_{(I,II)}$); 61.1, 61.3 ($C\text{-}11_{(I,II)}$); 109.3 ($C\text{-}2_{(II)}$); 110.4 ($C\text{-}2_{(I)}$); 115.8 ($C\text{-}6_{(I)}$); 116.9 ($C\text{-}6_{(II)}$); 123.7 ($C\text{-}4_{(I)}$); 124.5 (br, $C\text{-}4_{(II)}$); 127.3, 127.3, 127.5, 128.4 (*o*-$Ph_{(I,II)}$, *p*-$Ph_{(I,II)}$); 139.4, 140.1 (br) (*i*-$Ph_{(I,II)}$); 141.1 ($C\text{-}3_{(I,II)}$); 145.3 ($C\text{-}5_{(I,II)}$); 156.6 ($NCOO_{(I,II)}$); 162.8, 163.1 ($C\text{-}1_{(I,II)}$); 171.5, 172.0 ($COO_{(I,II)}$); IR (neat): $\tilde{\nu}$=3029 (w), 2978 (w), 1688 (s), 1657 (s), 1619 (m), 1570 (m), 1438 (m), 1360 (m), 1314 (s), 1261 (s), 1133 (m), 1048

(m), 943 (m), 881 (w), 804 (m), 698 (s), 582 (m), 528 (w) cm^{-1}; EIMS (EI, 70 eV): *m/z* (%)=371 (M^+, 2), 340 (9), 270 (8), 269 (35), 268 (19), 238 (10), 237 (55), 236 (23), 194 (14), 193 (76), 192 (100), 179 (18), 165 (41), 164 (53), 148 (86), 135(66), 120 (87), 91 (32), 77 (18), 42 (85); HRMS (ESI-TOF): calcd for $C_{42}H_{50}N_2NaO_{10}$ $[2M+Na]^+$: 765.33577; found: 765.33613.



*3.1.38. Ethyl-4-(2-(ethoxycarbonyl(methyl)amino)-2-phenylethyl)-2-hydroxy-6-methylbenzoate and ethyl-2-(2-(ethoxycarbonyl(methyl)-amino)-2-phenylethyl)-6-hydroxy-4-methylbenzoate (**12b**).* Starting with 1,3-bis(silyl enol ether) **5j** (600 mg, 2.18 mmol), ethyl methyl(3-oxo-1-phenyl-5-(trimethylsilyloxy)hex-4-enyl)carbamate **11** (792 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **12b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=23/2) as a slight orange oil (353 mg, 42%). ^1H NMR (500 MHz, $CDCl_3$, 300 K): δ=0.93–1.10 (br m, $6H_{(II)}$, H-$12_{(II)}$, H-$14_{(II)}$); 1.16 (t, ^3J=7.3 Hz, $3H_{(I)}$, H-$12_{(I)}$); 1.40 (t, ^3J=7.3 Hz, $3H_{(I)}$, H-$14_{(I)}$); 2.25 (s, $3H_{(II)}$, H-$10_{(II)}$); 2.50 (s, $3H_{(I)}$, H-$10_{(I)}$); 2.61 (s, $3H_{(II)}$, H-$9_{(II)}$); 2.63 (s, $3H_{(I)}$, H-$9_{(I)}$); 3.14–2.99 (m), 3.21 (dd, $^2J_{7a,7b}$=14.2 Hz, $^3J_{7,8}$=6.0 Hz), (H-$7_{(I,II)}$); 3.71–4.08 (br m, $3H_{(I)}$, $3H_{(II)}$, H-$11_{(I)}$, H-$7_{(I)}$, $OCH_{2(II)}$, H-$7_{(II)}$); 4.22–4.35 (m, $2H_{(II)}$, $OCH_{2(II)}$); 4.40 (q, $2H_{(I)}$, H-$13_{(I)}$); 5.60–5.78 (br m, $1H_{(I)}$, $1H_{(II)}$, H-$8_{(I,II)}$);6.44 (d, $^4J_{4,6}$=1.5 Hz, $1H_{(II)}$, H-$4_{(II)}$); 6.61 (br, $1H_{(I)}$, H-$4_{(I)}$); 6.70 (br, $1H_{(II)}$, H-$6_{(II)}$); 6.71 (br, $1H_{(I)}$, H-$6_{(I)}$); 7.25–7.39 (m, $5H_{(I)}$, $5H_{(II)}$, $Ph_{(I,II)}$); 11.36 (s, $1H_{(I)}$, $OH_{(I)}$); 11.45 (s, $1H_{(II)}$, $OH_{(II)}$); ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ=13.7, 14.2, 14.5 (C-$12_{(I,II)}$, C-$14_{(I,II)}$); 21.5 (C-$10_{(II)}$); 24.1 (C-$10_{(I)}$); 28.8 (C-$9_{(I)}$); 29.1 (br), 29.3 (br), (C-$9_{(II)}$); 36.2, 36.4, 36.5 (br), (C-$7_{(I,II)}$); 58.0 (C-$8_{(I)}$); 58.7 (C-$8_{(II)}$); 61.3 (C-$11_{(I)}$); 61.4 (C-$13_{(I)}$); 61.1, 61.6 (br), (C-$11_{(II)}$, C-$13_{(II)}$); 109.3 (br), 109.7 (br), (C-$2_{(II)}$); 110.6 (C-$2_{(I)}$); 115.8 (C-$6_{(I)}$); 117.0 (br, C-$6_{(II)}$); 123.7 (C-$4_{(I)}$); 124.2 (br), 124.7 (br), (C-$4_{(II)}$); 128.5, 127.5, 127.4, 127.4 (*o*-$Ph_{(I,II)}$, *m*-$Ph_{(I,II)}$, *p*-$Ph_{(I,II)}$); 139.5 (*i*-$Ph_{(I)}$); 140.0 (br), 140.2 (br), (*i*-$Ph_{(II)}$); 141.1 (br, C-$3_{(II)}$); 141.2 (C-$3_{(I)}$); 145.1 (C-$5_{(I)}$); 144.5 (br), 145.3 (br), (C-$5_{(II)}$); 156.6 (br), 156.8 (br), ($NCOO_{(I,II)}$); 162.9 (C-$1_{(I)}$); 163.3 (br, C-$1_{(II)}$); 171.3, 171.6 ($COO_{(I,II)}$); ^1H NMR (500 MHz, $CDCl_3$, 263 K, ratios of rotamers 0.53 (IA):0.47 (IB) and 0.62 (IIA):0.38 (IIB)): δ=0.92 (t, ^3J=7.3 Hz, $3H_{(IIA)}$, H-$12_{(IIA)}$); 0.99 (t, ^3J=7.3 Hz, $3H_{(IIA)}$, H-$14_{(IIA)}$); 1.00 (t, ^3J=7.3 Hz, $3H_{(IIB)}$), 1.06 (t, ^3J=7.3 Hz, $3H_{(IIB)}$), (H-$12_{(IIB)}$, H-$14_{(IIB)}$); 1.14 (t, ^3J=7.3 Hz), 1.16 (t, ^3J=7.3 Hz), ($3H_{(I)}$, H-$12_{(I)}$); 1.39 (t, ^3J=7.3 Hz), 1.41 (t, ^3J=7.3 Hz), ($3H_{(I)}$, H-$14_{(I)}$); 2.25 (s, $3H_{(IIB)}$, H-$10_{(IIB)}$); 2.29 (s, $3H_{(IIA)}$, H-$10_{(IIA)}$); 2.49 (s), 2.50 (s), ($3H_{(I)}$, H-$10_{(I)}$); 2.58 (s, $3H_{(IIA)}$, H-$9_{(IIA)}$); 2.59 (s, $3H_{(IIB)}$, H-$9_{(IIB)}$); 2.61 (s), 2.62 (s), ($3H_{(I)}$, H-$9_{(I)}$); 2.96 (dd, *J*=12.9 Hz, *J*=12.0 Hz, $2H_{(II)}$, H-$7_{(II)}$); 3.00–3.10 (m, $1H_{(I)}$, $1H_{(II)}$, H-$7_{(I)}$, H-$7_{(II)}$); 3.20 (ddd, ^2J=14.0 Hz, ^3J=9.8 Hz, ^3J=5.0 Hz, $2H_{(I)}$, H-$7_{(I)}$); 3.67–3.85 (m, $2H_{(II)}$, H-$11_{(II)}$); 3.68–4.07 (m, $3H_{(I)}$, $1H_{(II)}$, H-$7_{(I)}$, H-$7_{(II)}$, H-$11_{(I)}$); 4.18–4.34 (m, $2H_{(II)}$, H-$13_{(II)}$); 4.35–4.41 (m, $2H_{(I)}$, H-$13_{(I)}$); 5.63 (dd, ^3J=11.5 Hz, ^3J=2.8 Hz), 5.67 (dd, ^3J=10.8 Hz, ^3J=5.0 Hz), 5.75–5.79 (m), ($1H_{(I)}$, $1H_{(II)}$, H-$8_{(I)}$, H-$8_{(II)}$); 6.42 (d, ^4J=1.5 Hz, $1H_{(IIB)}$, H-$4_{(IIB)}$); 6.43 (d, ^4J=1.5 Hz, $1H_{(IIA)}$, H-$4_{(IIA)}$); 6.58 (br s), 6.66 (br s), ($1H_{(I)}$, H-$4_{(I)}$); 6.68 (br s, $1H_{(IIB)}$, H-$6_{(IIB)}$); 6.70 (br s, $1H_{(IIA)}$, H-$6_{(IIA)}$); 6.69 (br s), 6.72 (br s), ($1H_{(I)}$, H-$6_{(I)}$); 7.26–7.38 (m, $5H_{(I)}$, $5H_{(II)}$, Ph); 11.56 (s), 11.58 (s), ($1H_{(I)}$, $OH_{(I)}$); 11.65 (s, $1H_{(IIB)}$, $OH_{(IIB)}$); 11.66 (s, $1H_{(IIA)}$, $OH_{(IIA)}$); ^{13}C NMR (125 MHz, $CDCl_3$, 263 K): δ=13.5 (C-$14_{(IIB)}$); 13.6 (C-$14_{(IIA)}$); 14.0 (C-$12_{(IIA)}$); 14.1, 14.1 (C-$14_{(I)}$); 14.4, 14.5, 14.6 (C-$12_{(I)}$, C-$12_{(IIB)}$); 21.5 (C-$10_{(IIB)}$); 21.6 (C-$10_{(IIA)}$); 24.3, 24.4 (C-$10_{(I)}$); 28.5, 28.6 (C-$9_{(I)}$); 28.9 (C-$9_{(IIA)}$); 29.1 (C-$9_{(IIB)}$); 36.0, 36.0, 36.1 (C-$7_{(I)}$, C-$7_{(IIB)}$); 36.3 (C-$7_{(IIA)}$); 57.5, 57.6 (C-$8_{(I)}$); 58.1 (C-$8_{(IIB)}$); 58.2 (C-$8_{(IIA)}$); 61.0 (C-$11_{(IIB)}$); 61.1 (C-$11_{(IIA)}$); 61.3, 61.3 (C-$11_{(I)}$); 61.5, 61.6 (C-$13_{(I)}$); 61.6 (C-$13_{(IIA)}$); 61.7 (C-$13_{(IIB)}$); 108.9 (C-$2_{(IIA)}$); 109.4 (C-$2_{(IIB)}$); 110.2, 110.3 (C-$2_{(I)}$); 115.7, 115.8 (C-$6_{(I)}$); 116.8 (C-$6_{(IIB)}$); 116.9 (C-$6_{(IIA)}$); 123.6, 123.7 (C-$4_{(I)}$); 124.2 (C-$4_{(IIB)}$); 124.6 (C-$4_{(IIA)}$); 127.1, 127.2, 127.2, 127.4, 127.4, 127.5, 127.5, 127.5 (*o*-$Ph_{(I,II)}$, *p*-$Ph_{(I,II)}$); 128.3, 128.4, 128.4, 128.5 (*m*-$Ph_{(I,II)}$); 139.2 (*i*-$Ph_{(IIA)}$); 139.6 (*i*-$Ph_{(IIB)}$); 139.6, 139.9 (*i*-$Ph_{(I)}$); 140.8 (C-$3_{(IIB)}$); 140.9 (C-$3_{(IIA)}$); 141.2, 141.3 (C-$3_{(I)}$); 144.6 (C-$5_{(IIB)}$); 144.9, 145.1 (C-$5_{(I)}$); 145.3 (C-$5_{(IIA)}$); 156.3 ($NCOO_{(IIB)}$); 156.5 ($NCOO_{(IIA)}$); 156.7, 156.8 ($NCOO_{(I)}$); 162.7, 162.8 (C-$1_{(I)}$); 163.1 (C-$1_{(IIB)}$); 163.2 (C-$1_{(IIA)}$); 171.3 ($COO_{(IIB)}$); 171.4 ($COO_{(IIA)}$); 171.6, 171.7 ($COO_{(I)}$); IR (neat): $\tilde{\nu}$=3029 (w), 2978 (w), 1690 (s), 1652 (s), 1618 (m), 1570 (m), 1445 (m), 1397 (m), 1311 (s), 1259 (s), 1171 (m), 1095 (m), 1003 (m), 946 (w), 863 (w), 803 (m), 698 (s), 581 (m) cm^{-1}; EIMS (EI, 70 eV): *m/z* (%)=385 (M^+, 3), 340 (7), 283 (15), 282 (13), 266 (10), 238 (10), 237 (40), 236 (26), 194 (14), 193 (63), 192 (100), 165 (45), 148 (71), 120 (79), 91 (26), 77 (15), 42 (85); HRMS (ESI-TOF): calcd for $C_{22}H_{26}NO_5$ $[M-H]^+$: 384.18165; found: 384.18236.

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References and notes

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